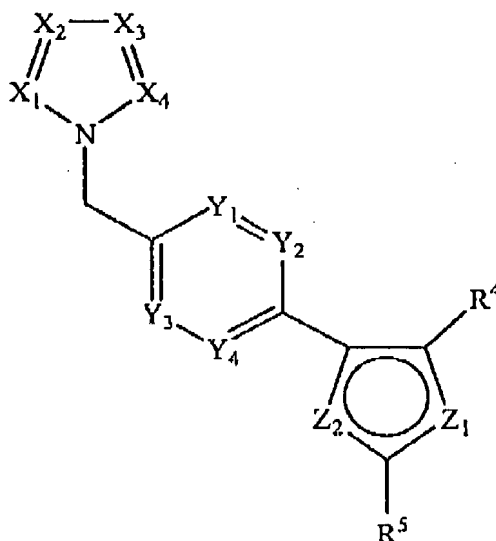


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Application No. 10/721,892
Response to Office Action mailed March 12, 2007
Atty. Dkt. No.: E072,1010.1CLAIMS

This listing of claims will replace all prior versions, and listings of claims in the application.

1. (Currently Amended) A compound of formula I,



wherein

one of X₁ represents -C(R¹)- and X₂ represents -N- and the other represents -C(R²)-;

X₃ represents -N- or -C(R²)-;

X₄ represents -N- or -C(R³)-;

R¹ represents H, and R² and R³ independently represent H, C₁₋₆ alkyl, C₁₋₆ alkoxy,

C₁₋₆ alkoxy-C₁₋₆-alkyl or halo;

provided that, when X¹ represents -C(R¹)-, X₂ represents -C(R²)- and X₄

represents -C(R³)-, then R¹ represents H;

Y₁, Y₂, Y₃, and Y₄ independently represent -CH- or -CF-;

Z₁ represents -CH-, -O-, -S-, -N- or -CH=CH-;

Z₂ represents -CH-, -O-, -S- or -N-;

provided that:

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- (a) ~~Z_1 and Z_2 are not the same;~~
 (b) ~~when Z_1 represents $\text{CH}=\text{CH}$, then Z_2 may only represent CH or~~
 ~~N ; and~~
 (c) ~~other than in the specific case in which Z_1 represents $\text{CH}=\text{CH}$, and~~
 ~~Z_2 represents CH , when one Z_1 and Z_2 represents CH , then the~~
~~other represents O or S ;~~
 R^4 represents $-\text{S}(\text{O})_2\text{N}(\text{H})\text{C}(\text{O})\text{R}^6$, $-\text{S}(\text{O})_2\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^6$, or $-\text{C}(\text{O})\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^6$,
 or, when Z_1 represents $\text{CH}=\text{CH}$, R^4 may represent
 ~~$-\text{N}(\text{H})\text{S}(\text{O})_2\text{N}(\text{H})\text{C}(\text{O})\text{R}^7$ or $-\text{N}(\text{H})\text{C}(\text{O})\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^7$;~~
 R^5 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy- C_{1-6} -alkyl or di- C_{1-3} -
 alkylamino- C_{1-4} -alkyl;
 R^6 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy- C_{1-6} -alkyl, and
 C_{1-3} alkoxy- C_{1-6} -alkoxy, C_{1-6} alkylamino or di- C_{1-6} alkylamino; and
 R^7 represents C_{1-6} alkyl;
 or a pharmaceutically-acceptable salt thereof.

Claims 2-10. (Cancelled)

11. (Original) A compound as claimed in claim 1 wherein R^2 represents
 C_{1-3} alkyl, halo or H.

12. (Original) A compound as claimed in claim 11 wherein R^2 represents H or
 methyl.

13. (Original) A compound as claimed in claim 11 wherein R^2 represents H.

14. (Original) A compound as claimed in claim 1 wherein R^3 represents
 C_{1-3} alkyl, halo or H.

15. (Original) A compound as claimed in claim 14 wherein R^3 represents H.

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16. (Original) A compound as claimed in claim 1 wherein Y_1 , Y_2 , Y_3 and Y_4 all represent -CH-.

17 and 18. (Cancelled)

19. (Original) A compound as claimed in claim 1 wherein Z_2 represents -CH-.

20. (Original) A compound as claimed in claim 1 wherein R^4 represents $-S(O)_2N(H)C(O)R^6$.

21. (Original) A compound as claimed in claim 1 wherein R^5 represents *n*-butyl or *iso*-butyl.

22. (Original) A compound as claimed in claim 21 wherein R^5 represents *iso*-butyl.

23. (Presently Amended) A compound as claimed in claim 1 wherein, when R^4 represents $-S(O)_2N(H)C(O)R^6$, $-S(O)_2N(H)S(O)_2R^6$ or $-C(O)N(H)S(O)_2R^6$, then R^6 represents *n*-butoxymethyl, *iso*-butoxy or *n*-butoxy.

24. (Original) A compound as claimed in claim 23 wherein R^6 represents *n*-butoxy.

25. (Currently Amended) A compound as claimed in claim 1 wherein, when X_1 , X_3 and X_4 all represent -CH-, Y_1 , Y_2 , Y_3 and Y_4 all represent -CH-, Z_1 represents -S- or -CH=CH-, Z_2 represents -CH- and R^5 represents *n*-butyl or *iso*-butyl, then R^4 represents $-S(O)_2N(H)C(O)R^6$, in which R^6 represents -O-*n*-butyl, -O-*iso*-propyl, -O-*iso*-butyl or -CH₂-O-*n*-butyl.

26. (Currently Amended) A compound as claimed in claim 1, which is:

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N-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthio-phen-2-sulfonamide;
N-*iso*-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide;
N-*iso*-propyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide;
N-(butoxyacetyl)-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide;
N-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-butylthiophene-2-sulfonamide;
N-butyloxycarbonyl-2-(4-imidazol-1-ylmethylphenyl)-4-*iso*-butylbenzenesulfonamide;
~~*N*-butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-2-ylmethylphenyl)thiophene-2-sulfonamide;~~
~~*N*-butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide;~~
~~*N*-butyloxycarbonyl-3-(4-[1,2,4]triazol-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide;~~
N-(butylamino)carbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide;
N-butylsulfonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide;
N-butylsulfonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-carboxamide;
N-butyloxycarbonyl-4-butyl-2-(4-imidazol-1-ylmethylphenyl)benzenesulfonamide;
~~*N*-(2-methoxyethoxy)carbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide;~~
N-ethylloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide;
N-*tert*-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide;
N-butyloxycarbonyl-3-[4-(4-methylimidazol-1-ylmethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide;
~~*N*-butyloxycarbonyl-3-(4-pyrazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide;~~
~~*N*-butyloxycarbonyl-3-[4-(3-trifluoromethylpyrazol-1-ylmethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide;~~
N-(*N*-butyl-*N*-methylamino)carbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide; or

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N-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-(2-methoxyethyl)-thiophene-2-sulfonamide.

27. (Original) A pharmaceutical formulation including a compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

28-31 (Cancelled)

32. (Original) A pharmaceutical formulation including a compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, and an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

33. (Original) A kit of parts comprising components:

- (a) a pharmaceutical formulation including a compound as defined in Claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and
- (b) a pharmaceutical formulation including an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier, which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

34. (Original) A pharmaceutical formulation including a compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, and an angiotensin converting enzyme inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

35. (Original) A kit of parts comprising components:

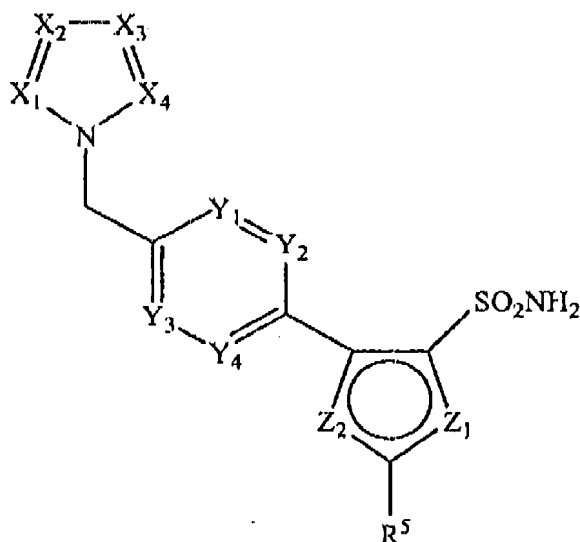
- (a) a pharmaceutical formulation including a compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, in admixture is with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

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- (b) a pharmaceutical formulation including an angiotensin converting enzyme inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier, which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

36. (Withdrawn/Currently Amended) A process for the preparation of a compound as defined in claim 1, which comprises:

- (i) for compounds of formula I in which R^4 represents $--S(O)_2N(H)C(O)R^6$ or $--S(O)_2N(H)S(O)_2R^6$, and R^6 is as defined in claim 1, reaction of a compound of formula II,

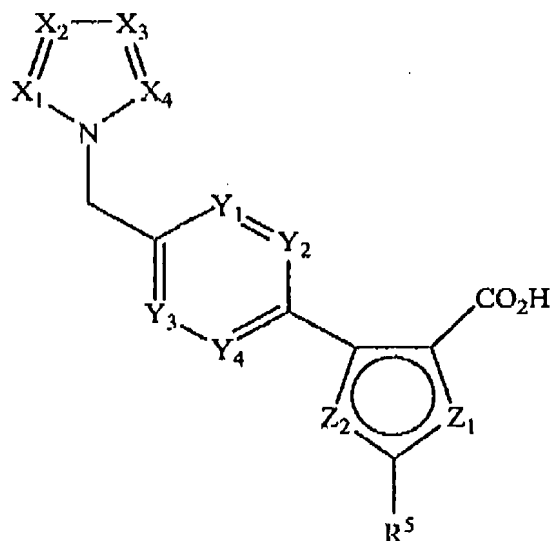


wherein X_1 , X_2 , X_3 , X_4 , Y_1 , Y_2 , Y_3 , Y_4 , Z_1 , Z_2 and R^5 are as defined in claim 1 with a compound of formula III, R^6GL^1 III wherein G represents $C(O)$ or $S(O)_2$ (as appropriate), L^1 represents a suitable leaving group and R^6 is as defined in claim 1;

- (ii) for compounds of formula I in which R^4 represents $--S(O)_2N(H)C(O)R^6$ and R^6 represents C_{1-6} alkoxy- C_{1-6} -alkyl, coupling of a compound of formula II as defined above with a compound of formula IV, $R^{6a}CO_2H$ IV wherein R^{6a} represents C_{1-6} alkoxy- C_{1-6} -alkyl;

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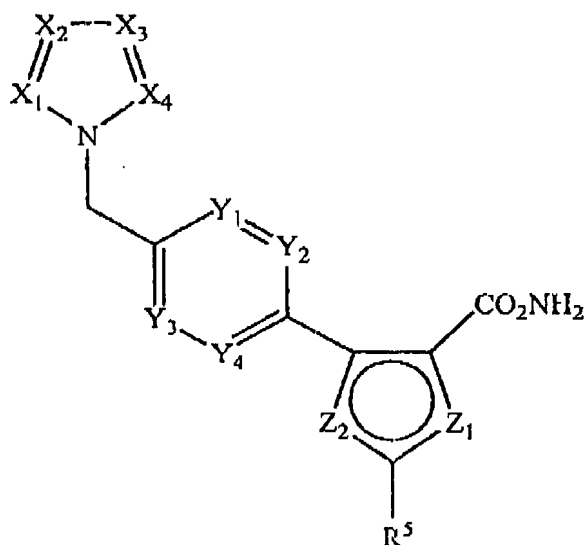
(iii) for compounds of formula I in which R^4 represents $--C(O)N(H)S(O)_2R^6$ and R^6 is as defined in claim 1, coupling of a compound of formula V,



wherein X_1 , X_2 , X_3 , X_4 , Y_1 , Y_2 , Y_3 , Y_4 , Z_1 , Z_2 and R^5 are as defined in claim 1, with a compound of formula VI, $R^6S(O)_2NH_2$ VI wherein R^6 is as defined in claim 1;

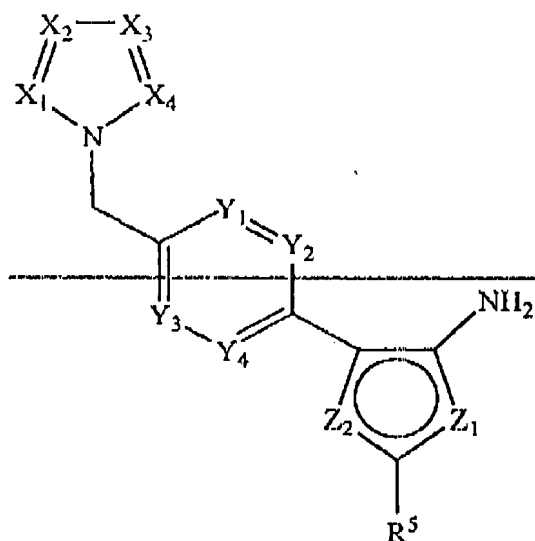
(iv) for compounds of formula I in which R^4 represents $--C(O)N(H)S(O)_2R^6$ and R^6 is as defined in claim 1, coupling of a compound of formula VII,

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wherein X₁, X₂, X₃, X₄, Y₁, Y₂, Y₃, Y₄, Z₁, Z₂ and R⁵ are as defined in claim 1, with a compound of formula VIII, R⁶S(O)₂Cl VIII wherein R⁶ is as defined in claim 1;

(v) for compounds of formula I in which R⁷ represents —N(H)S(O)₂N(H)C(O)R⁷ and R⁷ is as defined in claim 1, reaction of a compound of formula IX,



wherein ~~X₁, X₂, X₃, X₄, Y₁, Y₂, Y₃, Y₄, Z₁, Z₂~~ and R⁵ are as defined in claim 1, with a compound of formula X, R⁷C(O)N(H)S(O)₂Cl X wherein R⁷ is as defined in claim 1;

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(vi) for compounds of formula I in which R^4 represents $-N(H)C(O)N(H)S(O)_2R^7$ and R^7 is as defined in claim 1, reaction of a compound of formula IX as defined above with a compound of formula XI, $R^8S(O)_2N(H)C(O)OR^9$ XI wherein R^8 represents C_{1-6} alkyl and R^9 is as defined in claim 1; (vii) for compounds of formula I in which R^4 represents $-N(H)C(O)N(H)S(O)_2R^7$ and R^7 is as defined in claim 1, reaction of a compound of formula IX as defined above with a compound of formula XII, $R^8S(O)_2NCO$ XII wherein R^8 is as defined in claim 1; (viii) for compounds of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ and R^6 represents C_{1-6} alkylamino, reaction of a compound of formula II as defined above with a compound of formula XIII, $R^{6a}NCO$ XIII wherein R^{6a} represents C_{1-6} alkyl; or (ix) for compounds of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ and R^6 represents di- C_{1-6} alkylamino, reaction of a corresponding compound of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ and R^6 represents C_{1-6} alkoxy with a compound formula XIV, $R^{6c}N(H)R^{6d}$ XIV wherein R^{6c} and R^{6d} independently represent C_{1-6} alkyl.

37. (Withdrawn/Currently Amended) A compound of formula II as defined in claim 36 or a protected derivative thereof.

38. (Withdrawn/Currently Amended) A compound of formula II as claimed in claim 36, or a protected derivative thereof, wherein X_1 , X_2 , X_3 , and X_4 all represent $-CH-$, Y_1 , Y_2 , Y_3 , and Y_4 all represent $-CH-$, Z_1 represents $-S-$ or $-CH=CH-$, Z_2 represents $-Cl-$ and R^5 represents n-butyl or iso-butyl.

39. (Withdrawn/Currently Amended) A compound of formula V as defined in claim 36 or a protected derivative thereof.

40. (Withdrawn/Currently Amended) A compound of formula VII as defined in claim 36 or a protected derivative thereof.

Claims 41 -42. (Cancelled)

43. New) A method of treating cardiovascular disorders, comprising administering a compound of Claim 1 to a patient in need of treatment thereof, wherein the cardiovascular is selected from the group consisting of hypertension, cardiac hypertrophy, cardiac failure, atherosclerosis, arterial thrombosis, venous thrombosis, endothelial dysfunction, endothelial lesions, post-balloon dilatation stenosis, angiogenesis, microvascular dysfunction, angina,

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cardiac arrhythmias, claudicatio intermittens, preeclampsia, myocardial infarction, reinfarction, ischaemic lesions, and ncointima proliferation.